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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/811,140	03/29/2004	John Kevin Collins	P66880US2	8469

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EXAMINER	
GANGLE, BRIAN J	

ART UNIT	PAPER NUMBER
1645	

DATE MAILED: 11/16/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/811,140	COLLINS ET AL.	
	Examiner	Art Unit	
	Brian J. Gangle	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *42-63* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *42-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 January 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *3/29/2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment received 8/16/2005 is acknowledged.

Claims 42-63 have been added.

Claims 16-41 have been cancelled.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on applications filed in Ireland on 1/15/1999 and 9/20/1999. It is noted, however, that applicant has not filed a certified copy of the 990033, and 990782 applications as required by 35 U.S.C. 119(b).

Information Disclosure Statement

The information disclosure statement filed 3/29/2004 fails to comply with the provisions of 37 CFR 1.97, 1.98 and MPEP § 609 because form PTO-892 is not a proper listing of information submitted for consideration by the office. It has been placed in the application file, but the information referred to therein has not been considered as to the merits. Applicant is advised that the date of any re-submission of any item of information contained in this information disclosure statement or the submission of any missing element(s) will be the date of submission for purposes of determining compliance with the requirements based on the time of filing the statement, including all certification requirements for statements under 37 CFR 1.97(e). See MPEP § 609 ¶ C(1).

Election/Restrictions

Applicant's election without traverse of anti-inflammatory effects of 8/16/2005 is acknowledged. The restriction requirement is withdrawn.

Claims 42-63 are pending.

Currently, claims 42-63 are under examination.

Specification

The specification is objected to as failing to provide proper antecedent basis for the claimed subject matter. See 37 CFR 1.75(d)(1) and MPEP § 608.01(o). Correction of the

following is required: claim 42, dependent claims 43-52, claim 53, and dependent claims 54-63 are drawn to a method of testing the inflammatory effect of a probiotic material, wherein one step requires the addition of a probiotic material comprising or suspected of comprising an inflammatory agent. The specification only teaches addition of two species of bacteria as the probiotic material. There is no inflammatory agent associated with these bacteria thus they must themselves be the inflammatory agent. An inflammatory agent is one which causes inflammation (American Heritage Dictionary), therefore a probiotic comprising an inflammatory agent would have to cause inflammation. However, these bacteria are supposed to be probiotics, which by definition should be beneficial (MSN Encarta) and the specification teaches that probiotic bacteria should have an anti-inflammatory effect to be beneficial (example 4). Therefore the specification provides no antecedent basis for claims involving the addition of a probiotic material comprising an inflammatory agent. Further, if the probiotic is known to be inflammatory, there would be no need to use the method of the invention to test its inflammatory effect.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 42-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant

art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a written description rejection.

As to claim 42, dependent claims 43-52, claim 53, and dependent claims 54-63, claims 42 and 53 recite a method of testing the inflammatory effect of a probiotic material, wherein one step requires the addition of a probiotic material comprising or suspected of comprising an inflammatory agent. While an "inflammatory effect" can be considered an increase or a decrease in inflammation, an inflammatory agent is one which causes inflammation (American Heritage Dictionary). The specification only teaches addition of two species of bacteria as the probiotic material and lacks a definition of a "probiotic material". There is no inflammatory agent associated with these bacteria thus they must themselves be the inflammatory agent. A probiotic comprising an inflammatory agent would have to cause inflammation. However, these bacteria are supposed to be probiotics, which by definition should be beneficial (MSN Encarta) and the specification teaches that probiotic bacteria should have an anti-inflammatory effect to be beneficial (example 4). Therefore the claims are drawn to something which cannot exist and as such, one of skill in the art would not recognize that applicants had possession of the invention as instantly claimed.

As to claims 44 and 55, the claims are drawn to the method where the immune cells are of gastrointestinal, respiratory or genitourinary origin. There is no guidance in the specification as to how said cells are to be obtained or even what cells the claim is referring to. If the immune cells in question are the PBMC of claims 42 and 53, there is no guidance as to how cells of a particular origin should be separated from cells of other origins, how one would recognize these cells, or how these cells would differ from other PBMC. If the cells are immune cells that interact with epithelial cells, such as dendritic cells, there is no mention in the specification or the claims of how to obtain or to use these cells. Also, by definition, immune cells are of hematopoeitic origin (Cellular and Mol. Immunol., Abbas *et al.*, 2005, p. 25-26). The art does not teach immune cells of gastrointestinal, respiratory or genitourinary origin, therefore, one skilled in the art would not recognize that applicants had possession of the invention as instantly claimed.

Claims 42-63 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are directed to methods for testing the inflammatory effect of a probiotic material comprising:

(a) introducing a probiotic material comprising or suspected of comprising an inflammatory agent to a system which comprises (1) epithelial cells of gastrointestinal, respiratory, or genitourinary origin which interact with the immune system and (2) peripheral blood mononuclear cells and

(b) determining the change in an immunological marker in response to the probiotic material.

The specification teaches the introduction of *Lactobacillus salivarius* strain UCC118 and *Bifidobacterium longum infantis* strain UCC 35624 as probiotic material and the measurement of TNFα, IL-8, IL-1RA, IFNγ, IL-6, and IL-6 soluble receptor to test an inflammatory effect. The specification further teaches that addition of *Lactobacillus salivarius* strain UCC118 or *Bifidobacterium longum infantis* strain UCC 35624 to epithelial CaCo-2 cells incubated with PBMCs causes a decrease in TNFα production. Addition of *Bifidobacterium longum infantis* strain UCC 35624 to epithelial CaCo-2 cells incubated with PBMCs causes a decrease in IL-8 production. Addition of *Lactobacillus salivarius* strain UCC118 to epithelial CaCo-2 cells incubated with PBMCs causes an increase in IL-1RA and IFNγ production as well as an increase in IL-6 and IL-6 soluble receptor. The art teaches that inflammation is a complex reaction of the innate immune system in vascularized tissues that involves the accumulation and activation of leukocytes and plasma proteins at a site of infection, toxin exposure, or cell injury. Inflammation is initiated by changes in blood vessels that promote leukocyte recruitment (Cellular and Mol. Immunol., Abbas *et al.*, 2005, p. 490). There are numerous cytokines that mediate immune responses in a variety of ways that do not always correspond to inflammation. For example, of the molecules mentioned in the specification, TNFα, IL-8, IFNγ, IL-6, and IL-6 soluble receptor are pro-inflammatory molecules (Kupper, J. Clin. Invest., 86:1783-1789, 1990, p. 1784, col. 2; Mosmann *et al.*, Immunol. Today, 138:138-146, 1996, p. 138, col. 1; Standiford *et al.*, Infect.

Immun. 62:119-125,1994, p. 119, col. 1). IL-1RA is reported to be an anti-inflammatory molecule, however, example 4 of the specification of the instant application reported that upon testing of *Lactobacillus salivarius* UCC118, TNFα, IFNγ, and IL-1RA levels dropped while IL-6 and IL-6 soluble receptor increased. This shows that even among the immunological markers mentioned in the specification, measurement of these molecules is not indicative of inflammation. Further, claims 42 and 53 recite a method of testing the inflammatory effect of a probiotic material, wherein one step requires the addition of a probiotic material comprising or suspected of comprising an inflammatory agent. While an "inflammatory effect" can be considered an increase or a decrease in inflammation, an inflammatory agent is one which causes inflammation (American Heritage Dictionary). The specification only teaches addition of two species of bacteria as the probiotic material and lacks a definition of a "probiotic material". There is no inflammatory agent associated with these bacteria thus they must themselves be the inflammatory agent. A probiotic comprising an inflammatory agent would have to cause inflammation. However, these bacteria are supposed to be probiotics, which by definition should be beneficial (MSN Encarta) and the specification teaches that probiotic bacteria should have an anti-inflammatory effect to be beneficial (example 4). The art teaches that introduction of probiotics should lead to a decrease in inflammation, thus the method using an inflammatory agent that would necessarily lead to an increase in inflammation is not possible using a probiotic material that would lead to a decrease in inflammation. Further, the genus of immunological markers is very broad, including numerous cytokines, receptors, receptor agonists, antibodies, and immune cells including T cells, B cells, dendritic cells, monocytes, and granulocytes. Even temperature and swelling are indicative of inflammation and could be considered an immunological marker. Further, DeSimone *et al.* (Immunopharmacol. Immunotoxicol. 14:331-340, 1992) showed that treatment of subjects with *Bifidobacterium* and *Lactobacillus* led to a decrease in inflammation, however, they also found an increase in TNFα levels in some patients (p. 339). The art and specification together show that measurement of particular cytokines does not correlate with a particular inflammatory response and that *in vitro* results are not predictive of *in vivo* results or efficacy. Therefore, in view of the teachings of the art and specification, one of skill in the art would not be able to use the invention as claimed.

Claims 42-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 42, and dependent claims 43-52, claim 42 recites a system comprising epithelial cells which interact with the immune system and peripheral blood mononuclear cells. This limitation is unclear. Does applicant mean that the system comprises epithelial cells (which interact with the immune system) and PBMC; or does applicant mean that the system comprises epithelial cells, and that those cells interact with the immune system and PBMC?

As to claim 42, dependent claims 43-52, claim 53, and dependent claims 54-63, the preambles of claims 42 and 53 state that they are methods for testing the inflammatory effect of a probiotic material. However, the active steps of the methods do not accomplish this, they only show a change in an immunological marker, which is not necessarily indicative of inflammation. Clarification is respectfully requested.

As to claims 43 and 54, the claims recite the limitation "where in the cells which interact with the immune system and the PBMC are of matched origin." There is no definition in the specification as to "matched origin" and it is unclear what this term means. Are the cells from the same specie, same organism, or same site within the organism?

As to claims 44 and 55, the claims recite "wherein the cells of the immune system are of gastrointestinal, respiratory or genitourinary origin." It is unclear what cells are being referred to. The independent claims upon which claims 44 and 55 depend recite "epithelial cells which interact with the immune system" and "peripheral blood mononuclear cells." Are the immune cells of claims 44 and 55 the PBMC or the immune cells which are interacting with the epithelial cells, or are the PBMC the cells of the immune system? Further, immune cells are, by definition, of hematopoeitic origin (Cellular and Mol. Immunol., Abbas *et al.*, 2005, p. 25-26) and therefore cannot be of gastrointestinal, respiratory or genitourinary origin.

As to claim 42, dependent claims 43-52, claim 53, and dependent claims 54-63, claims 42 and 53 recite a method of testing the inflammatory effect of a probiotic material, wherein one step requires the addition of a probiotic material comprising or suspected of comprising an inflammatory agent. While an "inflammatory effect" can be considered an increase or a decrease in inflammation, an inflammatory agent is one which causes inflammation (American Heritage

Dictionary). A probiotic comprising an inflammatory agent would have to cause inflammation. However, these bacteria are supposed to be probiotics, which by definition should be beneficial (MSN Encarta) and the specification teaches that probiotic bacteria should have an anti-inflammatory effect to be beneficial (example 4). Therefore the claims are drawn to something which cannot exist.

As to claim 42, dependent claims 43-52, claim 53, and dependent claims 54-63, claims 42 and 53 recite probiotic material comprising an inflammatory agent. The specification only teaches addition of two species of bacteria as the probiotic material. Are the bacteria themselves the inflammatory agent, or is a separate agent to be included in the material?

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 42-44, 46-47, 49-50, and 52 are rejected under 35 U.S.C. 102(a) as being anticipated by Collins *et al.* (Gastroenterol. 116:G3058, April, 1999).

The claims are drawn to an *in vitro* method for testing the inflammatory effect of a probiotic material comprising introducing a probiotic material comprising introducing an inflammatory agent into a system comprising epithelial cells of gastrointestinal, respiratory or genitourinary origin which interact with the immune system and peripheral blood mononuclear cells; and determining the change in an immunological marker in response to the probiotic material, the cells which interact with the immune system being on a microporous support (claim

42). The claims include, as further limitations, said method wherein the cells which interact with the immune system and the PBMC are of matched origin (claim 43) and wherein the cells of the immune system are of gastrointestinal, respiratory, or genitourinary origin (claim 44). Limitations also include the immunological marker as a cytokine (claim 46), including TNFα (claim 47). Further limitations include the inflammatory effect as anti-inflammatory (claim 49) or pro-inflammatory (claim 50) and the probiotic material as *Lactobacillus* (claim 52).

As to claims 42-44, 46-47, 49-50, and 52, Collins *et al.* teach (see abstract) a method of testing the inflammatory effect of *Lactobacillus* where the probiotic material (*Lactobacillus*) is introduced into a system comprising epithelial cells (gastrointestinal mucosa) which interact with peripheral blood mononuclear cells, and determining the change in an immunological marker. The collagen and fibrous support of gastrointestinal epithelial cells is considered a microporous support. The epithelial cells and PBMC are matched as they are from the same organism, and the PBMC cells of the system include cells of gastrointestinal origin. Collins *et al.* teach the measurement of TNFα (a cytokine) as the immunological marker. The instant specification teaches that TNFα is a pro-inflammatory agent and that suppression of TNFα is an anti-inflammatory effect, therefore, measurement of TNFα includes both pro and anti-inflammatory effects. Since none of the components of the invention are isolated or purified, the system used to carry out the method can be interpreted as an organism and the term *in vitro* is given no patentable weight.

Claims 42-44, 46-47, 49-52 are rejected under 35 U.S.C. 102(b) as being anticipated by DeSimone *et al.* (Immunopharmacol. Immunotoxicol. 14:331-340, 1992).

As to claims 42-44, 46-47, 49-52, DeSimone *et al.* teach a method of testing the inflammatory effect of *Lactobacillus* and *Bifidobacterium* where the probiotic material is introduced into a system comprising epithelial cells (gastrointestinal mucosa) which interact with peripheral blood mononuclear cells, and determining the change in an immunological marker (p. 332-333, methods section). The collagen and fibrous support of gastrointestinal epithelial cells is considered a microporous support. The epithelial cells and PBMC are matched as they are from the same organism, and the PBMC cells of the system include cells of gastrointestinal origin. DeSimone *et al.* teach the measurement of TNFα (a cytokine) as the immunological

marker (p. 333, laboratory parameters). The instant specification teaches that TNFα is a pro-inflammatory agent and that suppression of TNFα is an anti-inflammatory effect, therefore, measurement of TNFα includes both pro and anti-inflammatory effects. Since none of the components of the invention are isolated or purified, the system used to carry out the method can be interpreted as an organism and the term *in vitro* is given no patentable weight.

Status of the Claims

All claims stand rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Gangle whose telephone number is 571-272-1181. The examiner can normally be reached on M-F 8:00 am - 4:30 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Lynette Smith can be reached on 571-272-0864.

The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

BG

Brian Gangle

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Patricia A. Duffy

PATRICIA A. DUFFY
PRIMARY EXAMINER